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The "original antigenic sin" and its relevance for SARS-CoV-2 (COVID-19) vaccination

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ABSTRACT

Imprinting of the specific molecular image of a given protein antigen into immunological memory is one of the hallmarks of immunity. A later contact with a related, but different antigen should not trigger the memory response (because the produced antibodies would not be effective). The preferential expansion of cross-reactive antibodies, or T-lymphocytes for that matter, by a related antigen has been termed the original antigenic sin and was first described by Thomas Francis Jr. in 1960. The phenomenon was initially described for influenza virus, but also has been found for dengue and rotavirus. The antibody dependent enhancement observed in feline coronavirus vaccination also may be related to the original antigenic sin. For a full interpretation of the effectivity of the immune response against SARS-CoV-2, as well as for the success of vaccination, the role of existing immunological memory against circulating corona viruses is reviewed and analyzed.

1. Introduction: the original antigenic sin

The first contact of the immune system with a foreign antigen, such as a surface protein of a given virus, surface protein 1 (SP1), will result in a primary immune response leading to generation of specific antibodies and cytotoxic T lymphocytes. During the primary response, a fraction of the specific B- and T-lymphocytes will differentiate into memory cells. The imprinting of the molecular image of SP1 into immunological memory is one of the hallmarks of immunity (and the underlying principle for vaccination as will be discussed below). A later contact with the same protein, which could be in the form of a second contact with the same virus, would trigger SP1 specific memory B- and T-lymphocytes and result in a faster, higher, and better immune response. A later contact with the same virus, but with a mutated SP1 protein (SP1a), the SP1 memory cells would not be triggered because of the specificity of antigen recognition by T- and B-cell receptors. SP1a thus will induce a primary immune response. But what would be the consequence if SP1 specific memory cells would be triggered by SP1a? The response would then be overwhelmed by anti-SP1 antibodies and cytotoxic T-lymphocytes. When these anti-SP1 antibodies would bind to SP1a, but not lead to virus neutralization, it would block and render the SP1a response ineffective (Fig. 1). This phenomenon has been termed the original antigenic sin and was first described by Thomas Francis Jr. in 1960, who coined this term with reference to the Biblical description of the original sin [1,2].

The original antigenic sin has special relevance for understanding the pathophysiology of SARS-CoV-2 infections leading to COVID-19 and even more so for (further) development and implementation of SARS-CoV-2 vaccines.

2. Original antigenic sin in the context of infection and vaccination

The original antigenic sin (OAS) concept was developed over half a century ago by Francis, based on his observation that influenza hemagglutination inhibition assay titers were highest against seasonal influenza strains to which specific age cohorts had first been exposed [1,3].

In the 1960′s the first generation of vaccines against Respiratory Syncytial Virus (RSV) were produced, in particular a formalin-inactivated alum-precipitated RSV vaccine. When this vaccine was injected intramuscularly in RSV-naïve infants, who later became naturally infected with RSV, a large proportion developed enhanced respiratory disease, in some cases with a fatal outcome. These dramatic events, interpreted as OAS, have been a major setback for RSV vaccine development [4].

The OAS in the context of infections has also been described for dengue [5,6], suggested for HIV [7] and for several other viruses.

As described above, the original antigenic sin was first postulated for antibodies, but the phenomenon later has also been described for T lymphocytes. In adults who are not (yet) exposed to malaria, T cells specific for malaria parasites and various malaria proteins, in particular circum-
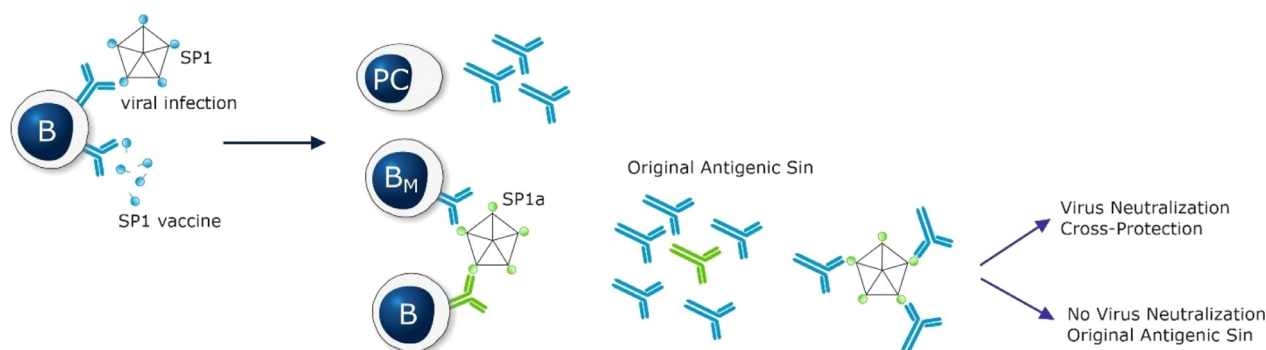
Fig. 1. Original Antigenic Sin, illustrated by the immune response to the viral protein SP1. During a primary response to SP1, either during a viral infection or vaccination with an SP1 containing vaccine, specific B cells response will generate plasma cells (PC), producing anti-SP1 antibodies as well as SP1 memory B cells (BM). A subsequent encounter with the same virus, but carrying a mutated SP1 protein, SP1a, will stimulate SP1a primary B cells and may also activate SP1 BM cells. Latter case, termed the original antigenic sin, will result in the production of large amounts of SP1 antibodies, which may bind to SP1a but could be functional inactive.
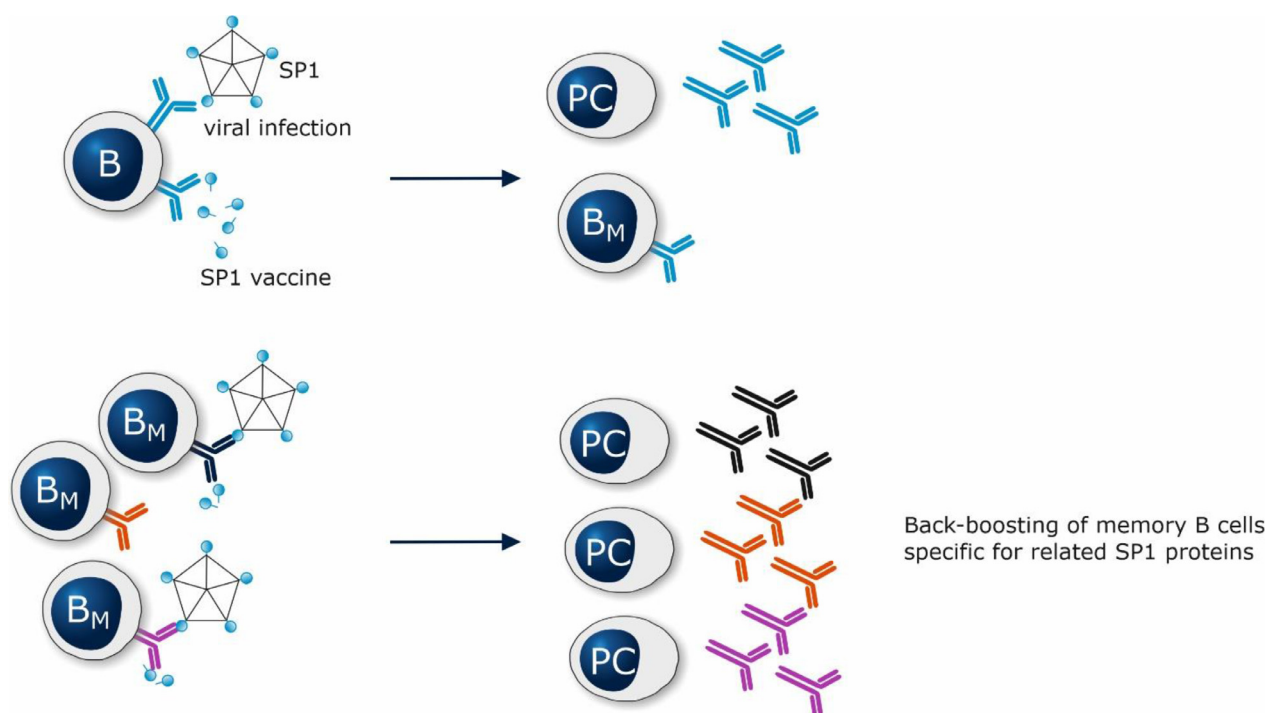

Fig. 2. Back boosting of memory B cells of conserved sequences of related proteins. Upper panel shows the specific response of SP1 specific B cells to infection or vaccination. The lower panel illustrates the activation of existing memory B cells against related SP1 proteins from 3 different but related viruses.

sporozoite protein, already can be demonstrated [8]. These (memory) T cells apparently have arisen through exposition to other (non-malaria) organisms, do cross-react but are unable to protect against malaria [8].

Unlike SARS-CoV-2 antibodies, SARS-CoV-2-reactive CD4+ T cells have been detected in unexposed individuals [9–13]. Epitope mapping showed that these preexisting memory CD4+ T cells are cross-reactive with similar affinity to SARS-CoV-2 as to circulating HCoV-OC43 and HCoV-HKU1 β coronaviruses but also to the HCoV-229E and HCoV-NL63 α coronaviruses [14]. It is unknown whether these T cells either positively or negatively contribute to severity of COVID-19.

It has been hypothesized that the original antigenic sin could also take place during SARS-CoV-2 infection and/or vaccination [15]. Indeed, the precise role of existing memory against the circulating coronaviruses (HCoV-HKU1, HCoV-NL63, HCoV-OC43, HCoV-229E) in reducing or increasing the risk for and /or severity of SARS-CoV-2 infection isn't totally clear. Because of widespread exposure of these coronaviruses, virtually everyone in the adult population has demonstrable

antibody levels. In The Netherlands, in a prospective study of newborns who were followed serologically from 0 to 20 months, it was found that HCoV-NL63 and HCoV43 infections occur quite frequently in early childhood. Exposure to these viruses may protect against subsequent infections with HCoV-229E and HCoV-HKU1, respectively [16].

3. Back boosting of existing memory

Back boosting is the term used for the activation of memory B cells against conserved sequences of related proteins from different bacteria or viruses Fig. 2. Aydillo et al. have described that during SARS-CoV-2 infection in hospitalized COVID-19 patients, there is also an increase in antibodies to conserved, but not variable, regions of HCoV-OC43 and HCoV-HKU1 β coronaviruses spike protein, so-called back-boosting [17]. Such a back-boosting effect was also described by Song et al. [18]. In our cohort, we have analyzed the antibody response to SARS-CoV-2 infection in severe COVID-19 patients, but did not find concomitant
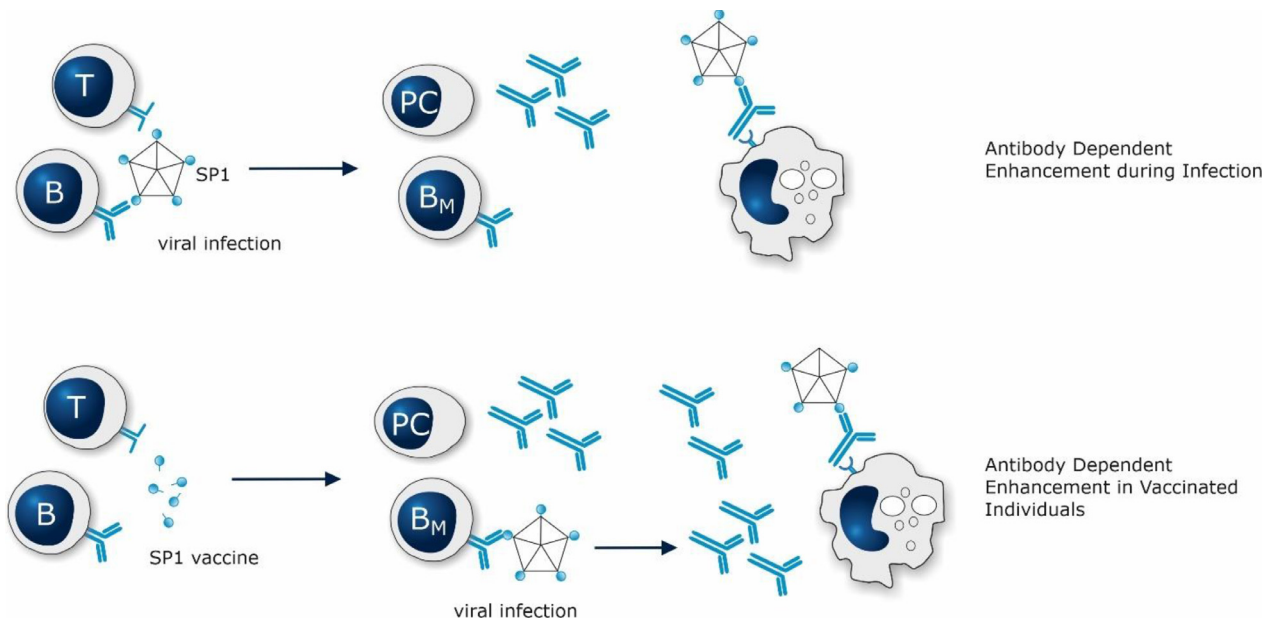
Fig. 3. Antibody dependent enhancement (ADE) of virus infection. Upper panel illustrates ADE during infection and the lower panel shows the mechanism of vaccination induced ADE.

substantial increase in antibody titers against spike S1 proteins from circulating β coronaviruses, nor α coronaviruses for that matter [19].

Amanat et al. have studied the impact of SARS-CoV-2 mRNA vaccination on antibodies to circulating coronaviruses [20]. Antibody titers against spike S1 protein from α-coronaviruses HCoV-229E and HCoV-NL63 were, as expected, already detectable pre-vaccination, but did not increase post-vaccination. However, titers against the spike proteins of β-coronaviruses HCoV-OC43 and HCoV-HKU1 increased substantially after vaccination. Subsequently, Amanat et al. generated panels of monoclonal antibodies (mAbs) from VH, Vκ, and Vλ genes which were PCR amplified from singly sorted plasmablasts [20]. Those mAbs target mostly spike S2 epitopes. Whether they (either in a positive or negative way) contribute to protection against SARS-CoV-2, HCoV-OC43, or HCoV-HKU1 infection is unknown as yet. While the authors conclude that their findings are an example of OAS, it can also be interpreted as back-boosting.

Back boosting can be considered a variation of the original antigenic sin, but from a different point of view. In the case of coronavirus, the memory B cells which are boosted by SARS-CoV-2 infection or vaccination would be memory B cells for the circulating HCoV-OC43 and HCoV-HKU1 β coronaviruses. Whether the produced antibodies would (either positive or negative) interfere with the (functionality of the) response to SARS-CoV-2 is unknown and could be dependent on the degree of antigenic relatedness (see below).

4. Antibody dependent enhancement

A related phenomenon, but distinct from the original antigenic sin, is antibody dependent enhancement (ADE). ADE is not equivalent to OAS because the antigen in priming and challenge is identical.

Antibody dependent enhancement is a phenomenon that already can take place during the course of a primary (SARS-CoV-2) infection (Fig. 3, upper row). Hoepel et al. have shown that the excessive inflammatory responses of alveolar macrophages during severe COVID-19 can be enhanced further by anti-spike S1 IgG antibodies [21]. This hyperactivation of macrophages only is induced when the antibodies are present in high titers and have a aberrant glycosylation pattern, particularly low degree of fucosylation of the antibody Fc tail. Fcγ receptor (FcγR) IIa and FcγRIII are the two primary IgG receptors responsible for the induction of COVID-19-associated cytokines such as IL-6 and TNF-α.[21]

The pathophysiological mechanism of ADE in case of a viral infection is that non-neutralizing antibodies, via Fc receptors, promote host cell entry of the virus, increase viral infectivity and worsen disease severity and outcome. ADE can thus occur for viruses with the capacity to replicate in macrophages such as coronaviruses.

There are two examples of diseases that make the development of effective and safe vaccines difficult or even impossible because of the occurrence of ADE. The first is dengue, where sequential infections show increasing severity based on ADE [22]. Vaccines against Feline Infectious Peritonitis virus, a corona virus, in cats are ineffective but even potentiate the disease based on ADE [23–26]. It has been speculated that also in SARS-CoV-1 and MERS infections in humans, the emerging immunopathology may be based on ADE [27]. Indeed, in vitro studies show that SARS-CoV-1 antibodies promote virus uptake into human macrophage and B cell lines [28]. Uptake of the virus is dependent on expression of FcγRII receptor on the respective cell lines [28]. A SARS-CoV-1 prototype vaccine tested in mice led to a clinical picture that may correspond to ADE.[29]

4. Conclusions and perspectives

From the data thus far, there are no indications that the current SARS-CoV-2 vaccines lead to ADE or that the effectivity would be impaired because of the OAS. Yet, sometimes (social) media reports hint towards a higher risk of SARS-CoV-2 infection following vaccination [30]. Furthermore, the concepts of OAS and ADE should be kept in mind when vaccines against novel SARS-CoV-2 variants are developed and tested, and the same would hold true for pan-coronavirus vaccines [31–33].

It should be realized that the effects of OAS not necessarily are negative, under some circumstances it can be beneficial because it can offer protection against antigenically related virus strains. Especially the back boosting aspect of OAS can have a relative protective effect when novel virus variants emerge, such as has been shown for influenza. Thus OAS could have conferred protection in the (very) old during the 2009 H1N1 "Swine Flu" pandemic because of their exposition to the 1918 H1N1 Spanish Flu strain [34–37]. The "antigenic distance hypothesis", developed by Smith et al. postulates that differences in (influenza) vaccine efficacy are due to the relative antigenic relatedness of the past vaccine strains, the current vaccine strains, and circulating epidemic strains [38]. Indeed, people infected with H1N1 influenza viruses dur-

ing childhood (and thus imprinted with that set of antigens/epitopes) were protected later in life against infections with a related virus such as H5N1 but not infections with more distantly related H3N2 [3,39,40].

When the Human Papilloma Virus vaccine was expanded from 2 serotypes with additional ones, concerns were raised that OAS could impair the effectivity of the augmented vaccines [41]. However, in a study comparing bivalent versus nonvalent HPV vaccines, no indications for OAS were found. Specifically, primary vaccination with HPV2 does not impair response to the additional HPV types present in the nonavalent HPV vaccine [42].

There was no evidence of ADE in pre-clinical SARS-CoV-2 challenge studies in rhesus macaques following immunization with 1 dose of ChAdOx1 nCoV-19 or 2 doses of the inactivated whole virus vaccine candidate BBIBP-CorV, both of which were protective in these studies [43,44].

Before the safety and efficacy of mRNA-SARS-CoV-2 vaccines was demonstrated in phase 3 studies, there was quite some speculation in the literature about the chance of success, given the above findings [45]. Kevin Morris was so convinced of ADE as an insurmountable obstacle that he considered it very unlikely (in June 2020) that there could be an effective and safe vaccine against SARS-CoV-2 in the short term [46]. It is striking that in a later publication (December 2020) in which he (correctly) calls for attention to the role of cellular immunity in the defense against SARS-CoV-2, the word ADE no longer appears in the paper and positive views are given about mRNA vaccines [47].

In summary, it can be concluded that phenomena such as OAS and ADE, based on theoretical grounds and well as outcome of experimental animal studies could have been stumbling blocks for the development of SARS-CoV-2 vaccines. In practice, current mRNA and as well as the adenovirus vectored vaccines appear to be safe and effective, with no signs of OAS or ADE.

The study of Amanat as discussed above has shown that mRNA vaccination can induce a modest but significant increase in antibodies to the related seasonal β-coronavirus spike proteins of HuCoV-OC43 and HuCoV-HKU1 [20]. The cross-reactive epitopes recognized by the antibodies that bind SARS-CoV-2, HuCov-HKU1, and HuCoV-OC43 spikes could form the basis for future pan-β-coronavirus vaccines. The original antigenic sin thus could turn into a virtue.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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